

REMARKS

The Examiner has objected to the Abstract. The Abstract has been written in amended form deleting the phrases objected to by the Examiner.

The Examiner has rejected Claims 1-11 and 13-31 under 35 USC 103 as being unpatentable over Ungs (5,866,561) in view of Reed et al. (6,197,013). The Examiner states that Ungs discloses a method of using estrogen compounds to reduce the risk of restenosis. However, Ungs does not disclose reducing the risk of restenosis, but discloses a method for inducing angiogenesis in blood vessels proximal to ischemic tissue or proximal to stenosed regions. The method includes application of an estrogen compound, e.g. 17beta-Estradiol, to the blood vessel wall at a treatment site proximal to or upstream of the stenosis. Preferred delivery devices are a doubled walled drug delivery catheter having porous outer walls or a drug injection device. Ungs mentions in Column 2, lines 44-46: "An estrogen compound could also be coated on a stent and placed at a desired delivery site, temporarily or permanently." No details of this are disclosed and nothing suggests that this be used to reduce complications after stent implantation as opposed to merely supplying a source of estrogen to induce angiogenesis.

Ungs deals with the problem of inducing angiogenesis. Angiogenesis means the growth of new blood vessels. The intention is that the new blood vessels shall bypass the stenosed part of the vessel, not heal it or prevent restenosis. The angiogenesis process is described e.g. at <http://www.angio.org/understanding/understanding.html>

The present invention does not deal with the problem of inducing angiogenesis, but with the problem of reducing complications after implantation of an intravascular stent, for example restenosis (Claim 1), or with the use of vessel healing substances (Claim 7). These are completely different problems which require different measures.

In order to induce angiogenesis, Ungs has to apply the 17beta-Estradiol (estrogen compound) at a treatment site proximal to or upstream of the stenosis. The present invention, however, applies the 17beta-Estradiol to the site of the intravascular stent placement, that means directly to the site of the stenosis.

Furthermore, for inducing angiogenesis, a very large amount of 17beta-Estradiol is required. That is why Ungs prefers delivery devices in form of a doubled walled drug delivery catheter or drug injection devices. It is not possible to coat a stent with enough 17beta-Estradiol in order to induce angiogenesis without replacing the stent frequently. When coating a stent, the outer diameter of the stent will increase by the thickness of the coated layer. The stent is retained in the vessel only by frictional forces between the stent and the vessel. When the 17beta-Estradiol is delivered, the outer diameter of the stent will decrease. If the thickness of the coated layer is too large, there is a risk that the stent will be released from the vessel.

Ungs teaching of inducing angiogenesis does not make it obvious that complications after normal stent implantation can be reduced by supplying 17beta-Estradiol to site of intravascular stent placement. This is different from supplying the 17beta-Estradiol to a blood vessel site to induce angiogenesis as taught by Ungs. In fact, Ungs says that his “invention is relatively more beneficial when practiced in smaller blood vessels when it is considered that smaller vessels are the vessels more likely to present difficulties in being crossed with balloon catheters and dilated, . . .” This would indicate that Ungs would not use his process in an area where a stent would normally be implanted to treat the problem, but would be used for those areas which would not normally otherwise be treated..

Concerning the subject matter of claims 14-31, the Examiner refers to Reed et al. (6,197,013) as teaching a CVD process for coating a stent. However, this is not taught by Reed

et al.. Reed et al. disclose a stent provided with probes which are cone shaped and have pointed tips (see Fig. 7 and column 5, lines 42ff). When the stent is inserted into a blood vessel, the probes penetrate the plaque and the interior wall of the blood vessel in order to deliver therapeutic agents (drug) placed on the probes to the vessel wall (see column 2, lines 23ff).

The stent is produced in several steps (see column 7, lines 5ff):

1. Fabrication of an uncoated metal stent provided with probes:

At first, a template wafer is fabricated from a crystalline silicon substrate (column 7, lines 6-8). The wafer is oxidized in a thermal oxidation furnace, so that a film of SiO_2 is grown on the surface (column 7, lines 43-46). A pattern is transferred into the SiO_2 layer (column 7, lines 52ff). Photoresist layers are applied to the wafer surface (column 7, lines 62ff). The wafer is exposed using a mask and exposure tool (column 8, lines 9ff). After development, the wafer is rinsed and dried (column 8, lines 41ff) and undergoes a hardbake (column 8, lines 63ff). The wafer is immersed in a solution of HF and water, hydrofluoric acid in order to transfer the patterns to the oxide layer (column 9, lines 7ff). The photoresist layers are removed using a convenient method (column 9, lines 20ff). The patterned wafer is etched in order to form the silicon probes (column 9, lines 27ff). The silicon wafer thus processed forms a template for building various embodiments of the intravascular delivery apparatus (column 9, lines 39ff).

Next, the silicon surface is coated with a sacrificial layer such as SiO_2 . This layer can be deposited using chemical vapor deposition (CVD) (column 9, lines 42ff). This is followed by thick layer of metal which can be deposited using a combination of evaporation, sputtering and electroplating (column 9, lines 51ff). The metal is patterned using the conventional photolithographic technique described above (column 9, lines 59ff). Next, the wafer is inserted into an etch bath for etching the sacrificial layer of SiO_2 until the patterned metal layer lifts off

from the underlying substrate resulting in a thin film of metal with pyramidal protrusions (column 10, lines 1ff). Finally, this film of metal (metal lattice) is rolled into a cylindrical shape and welded to form the cylindrical stent (column 10, lines 13 ff) resulting in an uncoated metal stent having probes.

Another method for making an uncoated metal stent having probes is to first fabricate a cylindrical mandrel with the probes on the surface (column 10, lines 62ff). The mandrel is coated (by electroplating, electroless deposition evaporation, or other techniques) by a conformal layer of metal (column 10, lines 65 ff). After removing the mandrel, the stent is released (column 11, lines 4-5).

2. Coating the stent with therapeutic agents:

After manufacture, the stent is sterilized and stored until ready for use (column 11, lines 62-63). When needed, the stent is coated with the desired drug or gene therapy material. This can be accomplished by dipping, spraying, spinning or rolling the stent with a liquid or gel containing the therapeutic material (column 11, lines 63ff).

Thus, the Reed et al. reference teaches using a CVD process for coating a silicon wafer with a sacrificial layer such as SiO_2 , but not for coating a stent with therapeutic agents. The use of a CVD process for coating wafers with an oxide layer is well known in the art. However, this technique has never been used for coating a stent with a therapeutic agent. Known methods for coating stents with therapeutic agents are dipping, spraying, spinning and rolling. Reed et al. mention these methods when describing the methods of coating. However, Reed et al. do not mention CVD as a method of coating stent with therapeutic agents.

The CVD process is not a well-known process in the art for coating a stent with a therapeutic agent. Therefore, it was not obvious that a CVD process could be used for coating the Unga stent.

Respectfully,

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A handwritten signature in black ink, appearing to read "Robert R. Mallinckrodt", written in a cursive style.

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Abstract of the Invention

[This invention relates to methods and arrangement for reducing complications]
Complications after implantation of an intravascular stent and, more particularly, [for reducing]
the risk of restenosis due to stent implantation [This is achieved by] is reduced by using 17beta-
estradiol as a vessel healing substance after implantation of an intravascular stent. The 17beta-
estradiol can be coated onto an intravascular stent and be included in a drug elution system
applied to the intravascular stent. This can be achieved by means of a surface coating process
such as a CVD process. 17beta-estradiol inhibits the growth of smooth muscle cells and
stimulates the re-endothelialization after implantation of an intravascular stent. The present
invention [makes use of these effects in order to prevent] reduces the risk of restenosis and in-
stent stenosis.